GOALS OF TREATMENT IN PATIENTS WITH PORTAL VEIN THROMBOSIS

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TREATMENT GOALS PVT BY SOCIETIES

Aim of treatment according to…

EASL

To prevent extension of thrombosis to mesenteric veins and thereby, mesenteric venous infarction and to achieve portal vein recanalization

AASLD

- In non-cirrhosis: To prevent thrombus extension to mesenteric veins; prevent intestinal ischemia; and, ideally, achieve recanalization to prevent development of portal hypertension.
- In cirrhosis: Not prevent portal hypertension development (that already exists), but to prevent worsening of PH and avoid progression of thrombosis that may hinder a future LT.

Baveno VII

- In non-cirrhosis: Recent PVT rarely resolves spontaneously. Therefore, at diagnosis, anticoagulation should be started immediately at a therapeutic dosage.
- In cirrhosis: In potential liver transplant candidates, the goal is to prevent re-thrombosis or progression of thrombosis to facilitate adequate portal anastomosis in liver transplantation and reduce post-transplant morbidity and mortality

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EASL guideline vascular liver diseases 2016; Northup et al. AASLD guidance paper 2021; Baveno VII consensus J Hep 2022

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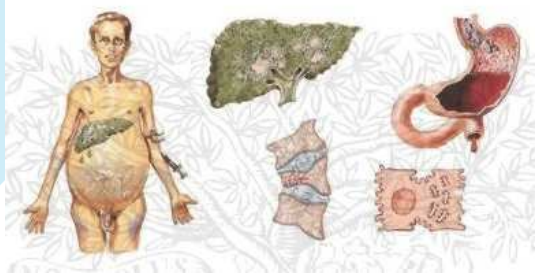


Cirrhosis

Non-cirrhosis

Decompensation

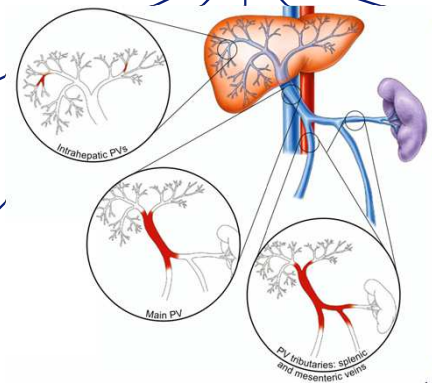
Hepatic encephalopathy

Ascites

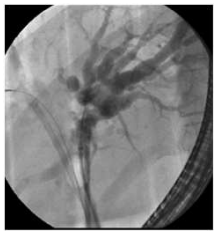
Varices / variceal bleeding

Portal vein thrombosis

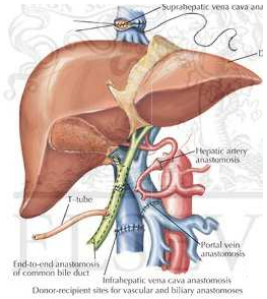
Survival



Portal cholangiopathy



LT suitability



Post LT outcomes

Bowel Ischaemia

Northup et al. Hep 2021; Sarawat et al. J Clin Exp Hep 2014; Zohdy et al. Obstet Gyn cases rev 2020; Netter

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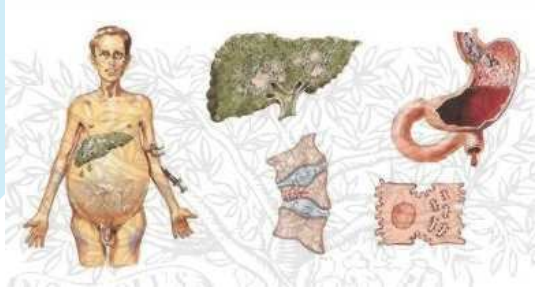

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RECANALIZATION

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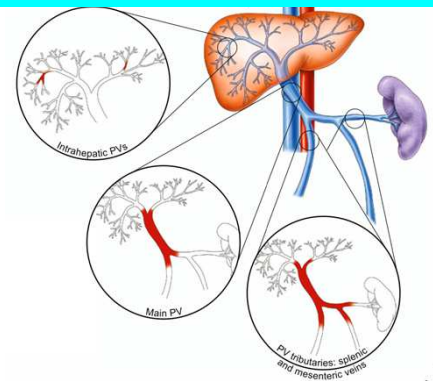
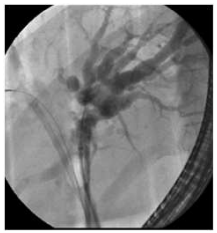


Portal biliopathy



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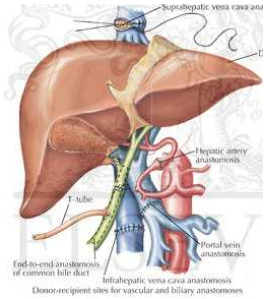

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RECANALIZATION DEFINITIONS USED

Study	Non-Cirrh vs Cirrh	Definition recanalization or study endpoint
Plessier et al. 2010	NC	Endpoint 1 = patency of PV trunk AND at least one of main, R or L branch Endpoint 2 = patency of SMV + SV
Condat et al. 2000 Turnes et al. 2008	NC	Complete recanalization = patency portal trunk AND one or both of 2 main branches AND splenic vein Partial recanalization = patency portal trunk AND at least 1 of its main branches OR splenic vein OR sup mesenteric vein
Mansour et al. 2022	NC, endovasc Rx	Technical success = complete recanalization of the entire portal venous system or complete bypass of the thrombus by TIPS Partial succes = residual thrombus causing <25% decrease in lumen
Ageno et al. 2015	NC + C	Recurrent SVT = thrombus extension or occurrence in previously patent segment
Chen et al. 2016	C	Improvement = decrease in grade of thrombus lumen occlusion and the absence of thrombus extension Progression = an increase in the grade and/or in the extension of PVT. Stable = no changes in degree grade and extension.
Francos et al. 2005	C	Complete recanalization = absence of intravascular in addition to restored blood flow
Senzolo et al. 2012	C	Endpoint 1 = complete or >50% patency of previously thrombosed PV trunk or main branches; Endpoint 2 =maintained patency of superior mesenteric vein and splenic veins
Chung et al. 2014	C	Complete resolution = disappearance of all evidence of thrombosis, as determined by transverse CT images. Partial resolution = at least 30% reduction in long diameter of main thrombus, that is, > 50% decrease in cross-sectional area without new thrombi.
Scheiner et al. 2018	C	Regression / resolution vs stable vs progression (not otherwise defined)
Senzolo et al. 2021	C	Complete recanalization = patency PV trunk OR main branches AND SMV AND SV. Partial = >50% recanalization PV trunk or branches.
La Mura et al. 2018	C	Complete recanalization of the previously detected thrombosis. Null responders = no change. Partial responders = all inbetween.
Delgado et al. 2012 Bergere et al. 2019	C C	Complete recanalization = patency of PV trunk AND ≥ 1 main IH branches AND SV AND SMV Partial recanalization = [patency of PV trunk AND ≥ 1 main IH branches] OR [SV (if thrombosed) and SMV (if thrombosed)] OR ≥ 50% reduction size thrombosis
Pettinari et al. 2018	C	Complete recanalization = patency of PV trunk AND branches AND SMV AND SV Partial recanalization = [≥ 50% reduction in thickness or length thrombus] OR [patency PV trunk AND recenalization of ≥ 1 of main PV branches or SV or SMV]

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META ANALYSES EFFECT OF ANTICOAGULATION ON RECANALIZATION

Loffredo et al. 2017

Complete recanalization of PVT

Study name	Odds ratio	Lower limit	Upper limit	P-value	Anticoagulant treatment	No treatment	Relative weight
Francoz	15,522	0,794	303,254	.071	8 / 19	0 / 10	6,60
Senzolo	10,435	1,245	87,473	.031	12 / 35	1 / 21	12,44
Garcovich	1,750	0,400	7,664	.458	7 / 15	5 / 15	23,90
Chung	2,750	0,524	14,439	.232	6 / 14	3 / 14	19,53
Wang	2,035	0,595	6,953	.257	26 / 31	23 / 32	32,50
Cai	39,000	1,277	1190,838	.036	4 / 5	0 / 6	5,04
	3,385	1,553	7,376	.002	63 / 119	32 / 98	

Odds ratio and 95% CI

0,01 0,1 1 10 100

Favours no treatment Favours anticoagulant treatment

Davis et al. 2019

Study or Subgroup	Intervention Events	Intervention Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
1.1.1 Anticoagulation							
Francoz 2005	8	19	0	10	4.3%	15.52 [0.79, 303.25]	2005
Senzolo 2012	12	33	1	21	8.4%	11.43 [1.36, 96.16]	2012
Chung 2014	6	14	3	14	13.9%	2.75 [0.52, 14.44]	2014
Chen 2016	15	22	4	16	18.4%	6.43 [1.52, 27.24]	2016
Subtotal (95% CI)		**88**		**61**	**45.1%**	**6.00 [2.38, 15.07]**	
Total events	41		8				

Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 3 (P = 0.65); I² = 0%

Test for overall effect: Z = 3.81 (P = 0.0001)

Odds Ratio M-H, Random, 95% CI

Ghazaleh et al. 2021

Study or Subgroup	Anticoagulation Events	Anticoagulation Total	No anticoagulation Events	No anticoagulation Total	Weight	Risk Ratio M-H, Random, 95% CI
Chen 2015	15	22	4	16	7.8%	2.73 [1.11, 6.68]
Chung 2014	11	14	5	14	10 9%	2.20 [1.03, 4.68]
Copaci 2016	31	50	12	44	22.2%	2.27 [1.34, 3.86]
Garcovich 2011	7	15	5	15	7.7%	1.40 [0.57, 3.43]
Noronha Ferreira 2019	18	35	6	32	10.0%	2.74 [1.25, 6.04]
Risso 2014	37	50	8	20	19.7%	1.85 [1.06, 3.24]
Scheiner 2018	7	12	10	36	12.3%	2.10 [1.03, 4.28]
Senzolo 2012	21	33	1	21	1.7%	13.36 [1.94, 92.7]
Tiwari 2018	20	25	4	20	7.7%	4.00 [1.63, 9.82]
Total (95% CI)		**256**		**218**	**100.0%**	**2.31 [1.80, 2.96]**
Total events	167					

Heterogeneity: Tau² = 0.00; Chi²= 7.47, df = 8 (P = 0.49); I² = 0%

Test for overall effect: Z= 6.57 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours no anticoagulation Favours anticoagulation

Rodrigues et al. 2018 – TIPS data

(C) *Overall 12-month portal vein recanalisation rate*

Study	Cases	Total	Prevalence	95% C.I.
Bauer 2006	8	9	0.89	[0.50; 0.98]
Han 2011	43	43	1.00	[0.84; 1.00]
Luca 2011	28	67	0.42	[0.31; 0.54]
Luo J 2011	10	11	0.91	[0.56; 0.99]
D'Avola 2012	15	15	1.00	[0.65; 1.00]
Chen 2015	4	5	0.80	[0.31; 0.97]
Luo X 2015	24	37	0.65	[0.48; 0.78]
Rosenqvist 2016	14	19	0.74	[0.50; 0.89]
Lakhoo 2016	6	9	0.67	[0.33; 0.89]
Wang 2016	49	63	0.78	[0.66; 0.86]
Klinger 2017	9	16	0.56	[0.32; 0.78]
Lv 2017	20	22	0.91	[0.70; 0.98]
Thornburg 2017	55	60	0.92	[0.81; 0.96]
Random Effects Model Pooled proportion			0.79	[0.67; 0.88]

Heterogeneity: I^2 = 78%, τ^2 = 0.9236, P < 0.01

0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Proportion of Recanalisation

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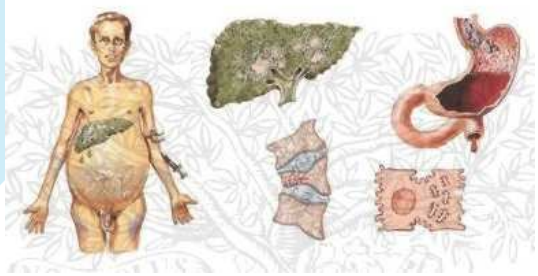
Loffredo et al. Gastro 2017; Davis et al. Clin Appl Thromb/Hemost 2019; Ghazaleh et al. Ann Gastro 2021; Rodrigues et al. AP&T 2018



Cirrhosis

Non-cirrhosis

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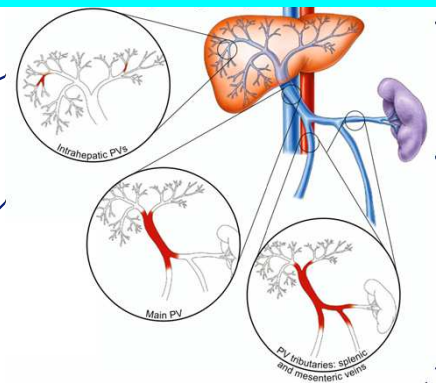
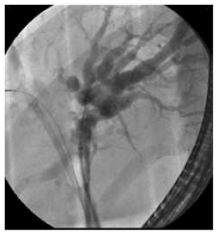


Portal biliopathy



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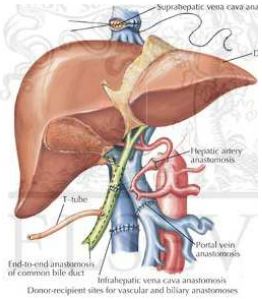

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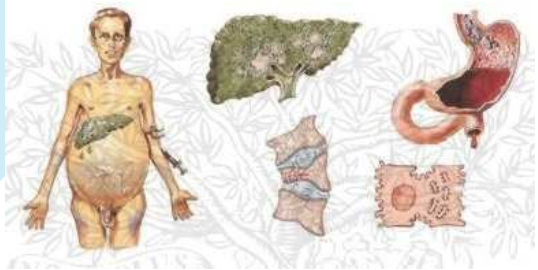

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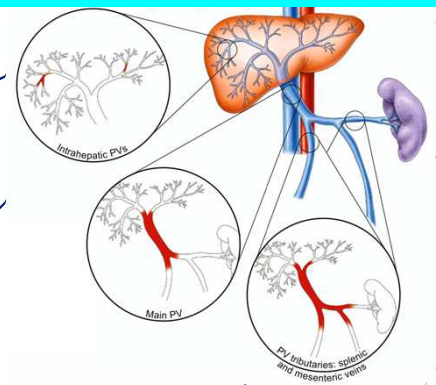

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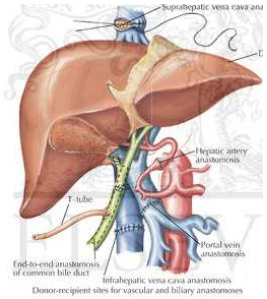

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PREVENTION OF VARICEAL BLEEDING

Non-cirrhotic PVT

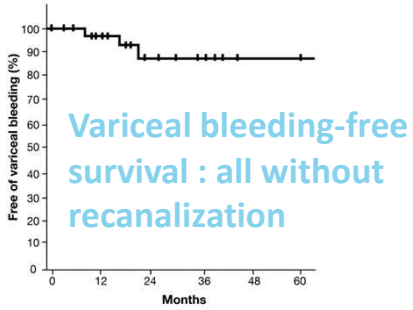
Plessier et al. Hepatology 2008

7/95 (7%) PVT on AC developed GI bleeding (38% recanalized; no comparison)

Turnes et al. Clin Gastro Hep 2008

N=38 PVT of whom N=27 (71%) AC, of whom 12/27 (44%) achieved recanalization

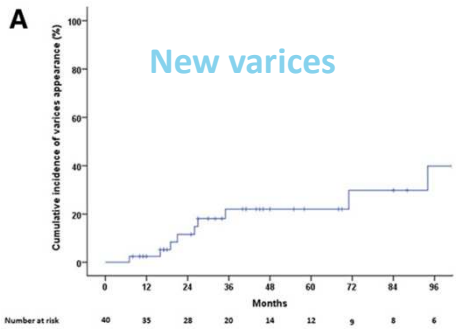
- **Varices developed in 8% with recanalization vs 64% without recanalization**
- **Variceal bleeding in 0% with recanalization vs 15% without recanalization (P=.06)**

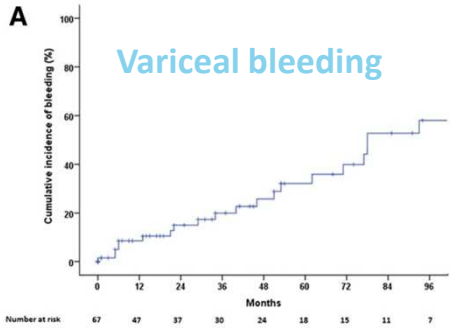


Ferreira, Seijo et al . Hepatology 2016

N=178 chronic PVT **without recanalization**

- 22% new varices at 5 years
- 30% bleeding at 5 years





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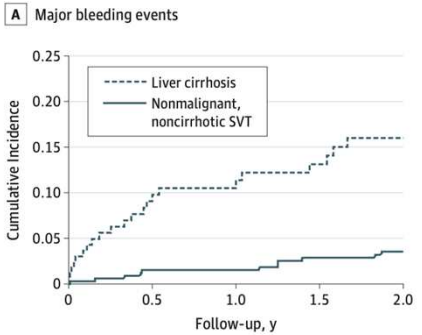
PREVENTION OF VARICEAL BLEEDING

Cirrhotic PVT – only safety data on AC

Ageno et al. JAMA Int Med 2015

Prospective study ISTH; N=604 SVT with or without cirrhosis, of whom 77% received AC

- All-cause major bleeding in cSVT 15% at 2 y vs 3% ncSVT
- Incidence 3.9 $_{\text{per 100py}}$ with AC vs 5.8 $_{\text{per 100py}}$ without AC



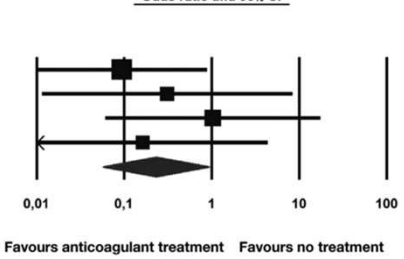
Pettinari et al. Am J Gastr 2018

N=182 PVT; AC in 44%; complete recanalization in 67% of AC and 25% in non-AC

- Variceal bleeding in 21.8% without AC vs 19.7% in AC (P=.85)

Loffredo et al. Gastro 2017 – Meta-analysis AC

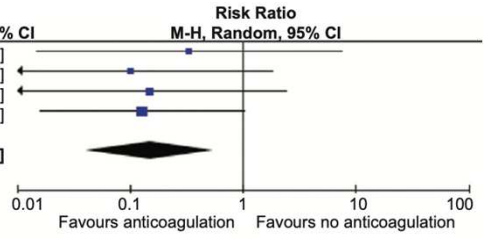
Study name	Statistics for each study				Events / total	
	Odds ratio	Lower limit	Upper limit	*P*-value	Anticoagulant treatment	No treatment
Senzolo	0,094	0,010	0,873	.038	1 / 35	5 / 21
Chung	0,310	0,012	8,292	.485	0 / 14	1 / 14
Wang	1,033	0,062	17,282	.982	1 / 31	1 / 32
cai	0,164	0,006	4,358	.280	0 / 5	2 / 6
	0,232	0,058	0,939	.041	2 / 85	9 / 73



Ghazaleh et al. Ann Gastr 2021 – Meta-analysis

Study or Subgroup	Anticoagulation Events	Total	No anticoagulation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chung 2014	0	14	1	14	17.6%	0.33 [0.01, 7.55]
Noronha Ferreira 2019	0	35	4	32	20.6%	0.10 [0.01, 1.82]
Scheiner 2018	0	12	9	36	22.2%	0.15 [0.01, 2.40]
Senzolo 2012	1	33	5	21	39.6%	0.13 [0.02, 1.01]
Total (95% CI)		**94**		**103**	**100.0%**	**0.15 [0.04, 0.55]**
Total events	1		19			

Heterogeneity: Tau²= 0.00; Chi²= 0.35, df= 3 (P = 0.95); I²= 0%
Test for overall effect: Z= 2.85 (P = 0.004)



PREVENTION OF DECOMPENSATION

Cirrhotic PVT

Nery et al. Hepatology 2015

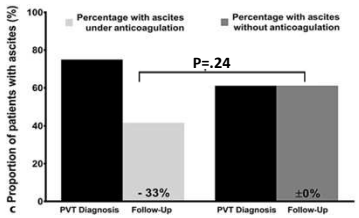
- N=1243 of whom N=118 PVT, only 6/118 (5%) AC
- No data on recanalization
- PVT did not impact hepatic decompensation

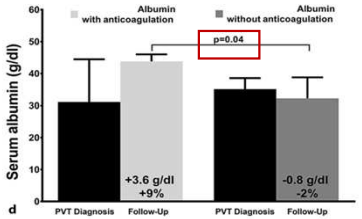
Table 3. Impact of Portal Vein Thrombosis (PVT) on Liver Disease Progression and Decompensation

	Univariate Models Unadjusted Estimates			Multivariate Models Adjusted for the Baseline Prognostic Variables*		
Models		HR	95% CI	*P*	HR	95% CI	*P*
Liver disease progression							
- Partial PVT	1.58	1.02-2.45	0.04	1.51	0.73-3.14	0.27	
- Partial or Complete PVT	1.48	0.97-2.26	0.067	1.32	0.68-2.55	0.41	
Decompensation							
- Partial PVT	1.77	1.07-2.92	0.027	1.60	0.69-3.74	0.28	
- Partial or Complete PVT	1.61	0.98-2.62	0.058	1.37	0.62-3.03	0.44	

Delgado et al. Clin Gastro Hep 2012

- N=55 with AC, complete recanalization in 45%
- **N=13 decompensation: 15% in recanalized and 25% in non-recanalized (P=.01)**



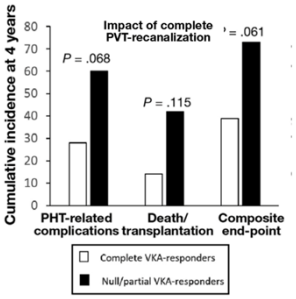


Scheiner et al. Wien Klin Wochenschr 2018

- N= 51 of whom 25% AC
- No data on recanalization
- Ns impact on ascites but significant improvement albumin

La Mura et al. Clin Gastro Hep 2018

- N=63 on AC, 50% complete recanalization
- **Trend less decompensation (PH events)**
- **Significant lower composite endpoint (death + events)**



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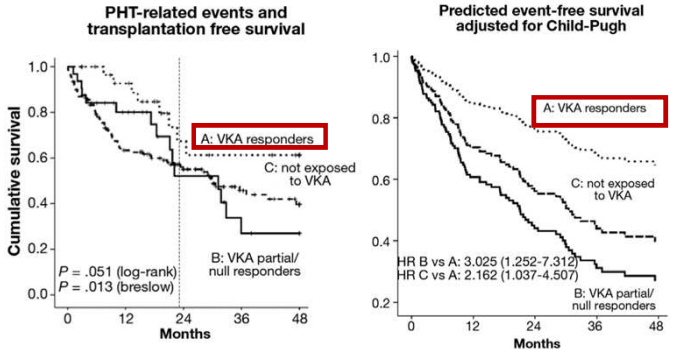
RECANALIZATION AND SURVIVAL

Cirrhotic PVT

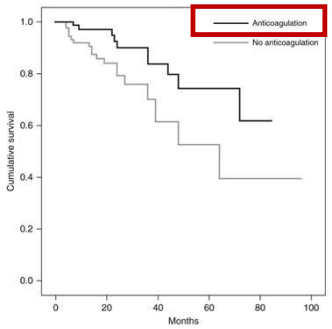
La Mura et al. Clin Gastr Hep 2018

- **Recanalization increased survival, independent of CP class**



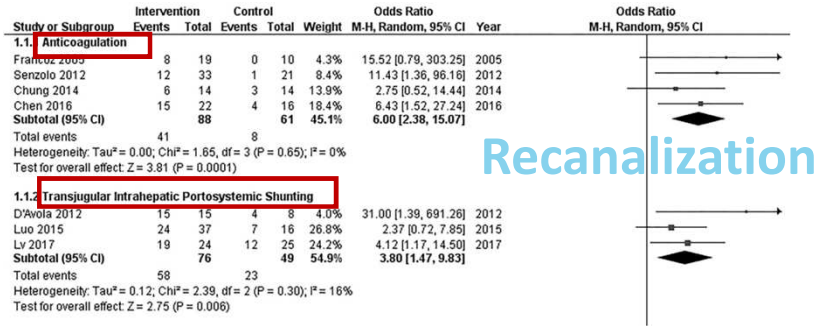
Pettinari et al. Am J Gastro 2019

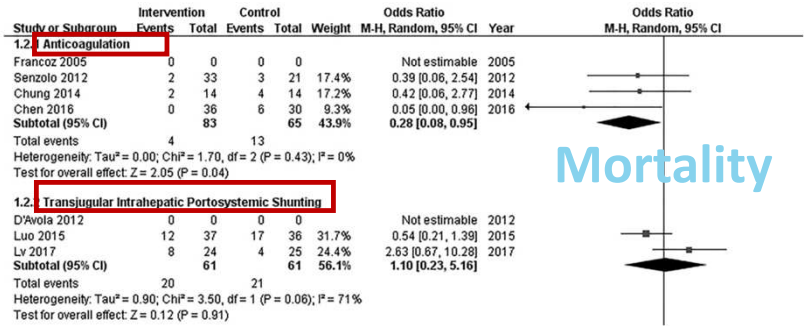
- N=81/182 (45%) AC; 67% recanalization on AC and 26% spontaneous
- Survival significantly better in AC group (p=0.01)



Davis et al. Clin Appl Thromb Hemost 2019

- Meta analysis effect of AC in cPVT
- Although AC and TIPS lead to recanalization, survival only better in AC





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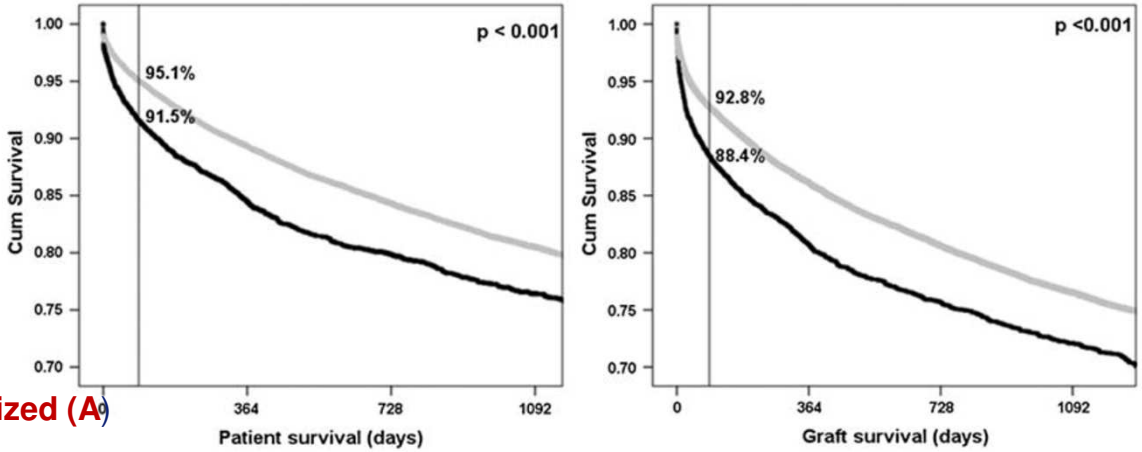
LIVER TRANSPLANTATION OUTCOMES

Cirrhotic PVT

Ghabril et al. Transplantation 2016

- OPTN database N=3321 cPVT at LT surgery (6.6%)
- Poorer patient and graft survival in 1st 90 days
- cPVT was no longer present at LT in 40% (i.e. recanalized)



- **Recanalized PVT (B) had similar PS and GS as non-recanalized (A)**

but lower PS and GS compared to never PVT (D)

	PVT at listing and at transplant group A, n = 969	*P* value group A versus B	PVT at listing but no PVT at transplant group B, n = 634	*P* value group B versus D	*P* value group A versus C	No PVT at listing but reported PVT at transplant group C, n = 2205	*P* value group C versus D	No PVT at listing or transplant group D, n = 42,363
Waitlist time, d	55 (11-205)	0.2	45 (9-192)	<0.001	<0.001	130 (25-431)	<0.001	71 (15-242)
Listing MELD	18 (13-25)	0.6	18 (13-26)	<0.001	0.03	16 (12-22)	0.02	16 (12-24)
MELD at liver transplant	21 (15-29)	0.9	21 (15-29.5)	<0.001	<0.001	20 (14-28)	<0.001	19 (13-28)
MELD rate of change (MELD point per month)	0.16 (–0.13-1.69)	0.3	0.2 (–0.04 to 1.7)	0.4	0.07	0.23 (0-1.42)	0.008	0.16 (0-1.56)
90 d patient survival	89.6%	0.2	91.5%	0.001	0.1	91.4%	<0.001	94.5%
90 d graft survival	89.2%	0.2	91.3%	0.001	0.06	91.3%	<0.001	94.4%

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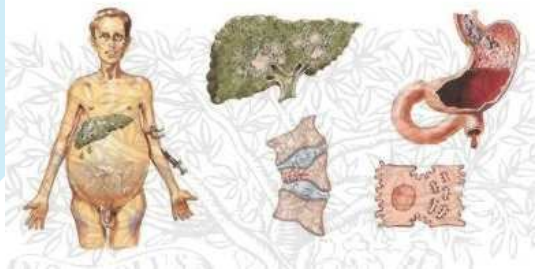


Cirrhosis

Non-cirrhosis

Ascites

Hepatic encephalopathy

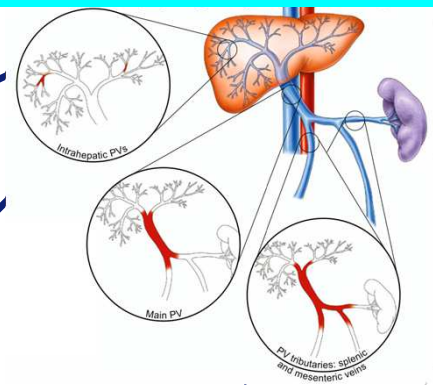
Decompensation

?

Varices / variceal bleeding

RECANALIZATION

Survival



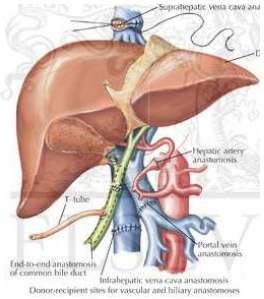
Portal biliopathy

?

LT suitability

?

Bowel Ischaemia



Post LT outcomes

Northup et al. Hep 2021; Sarawat et al. J Clin Exp Hep 2014; Zohdy et al. Obstet Gyn cases rev 2020; Netter

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IS RECANALIZATION THE END GOAL?

Answer: NO

Three reasons:

1. Recanalization occurs only in 38%-80% of non-cirrhotic PVT and 44% (15%-100%) in cirrhotic PVT

2. We have to show that recanalization indeed results in the expected therapeutic effect (i.e. efficacy)

3. After recanalization is achieved, rethrombosis may occur in 18-38% in ncPVT and 27-70% in cPVT

Plessier et al. Hepatology 2010; Turnes et al. Clin Gastro Hep 2008; Chen et al. Liver Transpl 2016

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CONCLUSION ON AVAILABLE DATA

- Recanalization is not the end goal of treatment
- We need an uniform definition for recanalization
  - Which level of recanalization results in reduction of clinical endpoints?
- Larger studies needed to show impact of treatment on relevant clinical endpoints

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